

Catalytic α -hydroxy carbon radical generation and addition. Synthesis of α -hydroxy- γ -lactones from alcohols, α,β -unsaturated esters and dioxygen

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A catalytic method for α -hydroxy carbon radical generation from alcohols has been developed and a convenient and synthetically useful approach to α -hydroxy- γ -lactones constructed.

Free radical reactions have attracted much attention in the synthesis of organic compounds because of their many advantages over ionic reactions, and therefore a variety of methodologies have been developed for the generation of carbon radicals.¹ To our knowledge, however, a limited number of methods, *e.g.* peroxide-^{1,2} and photo-^{1,3} initiated techniques and redox systems using metal ions,^{1,4} have been used for the generation of carbon radicals from alcohols. Therefore, we believe that the catalytic carbon radical formation from alcohols and its use in organic synthesis are of interest and very useful as a synthetic tool. However, such a method has, as yet, not been realized.

Recently, we have shown that phthalimide *N*-oxyl (PINO), generated from *N*-hydroxyphthalimide (NHPI) and dioxygen, can abstract the hydrogen atom from alkanes to form alkyl radicals which are readily captured by O₂ to give oxygenated compounds such as alcohols, ketones and carboxylic acids.⁵ As an application of this procedure, we report here, the first successful catalytic α -hydroxy carbon radical generation from alcohols using NHPI combined with cobalt species as the catalyst under O₂ (1 atm) and trapping the resulting α -hydroxy radicals by α,β -unsaturated esters leading to α -hydroxy- γ -lactones which are very difficult to obtain by conventional methods. Such lactones are very attractive as valuable synthetic precursors for species such as α,β -butenolides which have potent biological activity⁶ as well as fine chemicals which are expected to be widely used in chemical industry.⁷

An outline of our approach is shown in Scheme 1: (i) *in situ* generation of an α -hydroxy carbon radical Aa from an alcohol assisted by NHPI/Co(II) under O₂; (ii) the addition of the radical Aa to an α,β -unsaturated ester; (iii) trapping of the radical B by

O₂; (iv) the intramolecular cyclization of the resulting 1,3-diol C to yield α -hydroxy- γ -lactone 3.

Initially, the generation of an α -hydroxy carbon radical from isopropyl alcohol 1a and the trapping of this radical by methyl acrylate 2a were examined by the use of three different combined catalytic systems: NHPI/Co(OAc)₂ I, NHPI/Co(acac)₃ II and NHPI/Co(OAc)₂/Co(acac)₃ III under O₂ (1 atm) at 60 °C, leading to α -hydroxy- γ,γ -dimethyl- γ -butyrolactone 3a in 27–78% yields (Fig. 1).† Inspection of Fig. 1 indicates that the reaction via catalyst I is terminated at an early stage and that catalyst II gives a higher yield of 3a, although an induction period of 3 h was observed. The Co(III) ion is well known to be gradually reduced to Co(II) by organic substrates via a one-electron transfer process.⁸ Therefore, it is thought that the induction period observed in the catalytic system II would correspond to the time required for the generation of Co(II) during the reaction. In order to shorten the induction period, we carried out the above reaction by adding a small amount of Co(II) ion [as Co(OAc)₂] to the NHPI/Co(III) system. As expected, a reduction of the induction period of the reaction was observed, and the best yield of 3a (78%) was obtained by the use of the catalytic system III. On the basis of these results, a variety of alkenes were treated with 1a under O₂ using the NHPI/Co(OAc)₂/Co(acac)₃ system (Table 1).

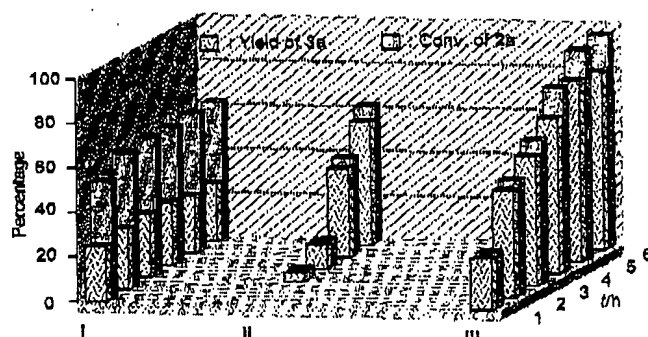
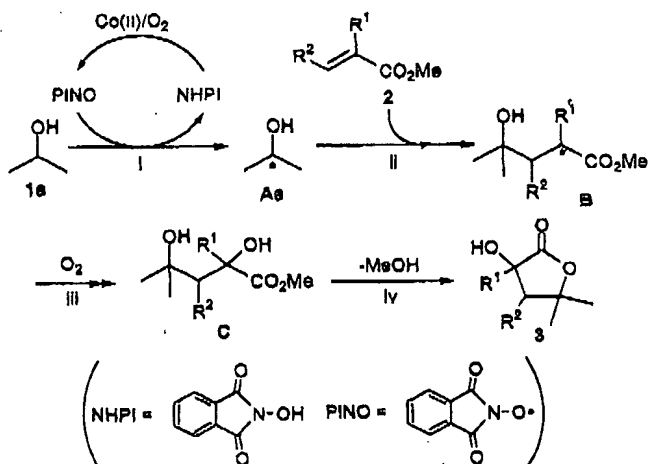


Fig. 1 Time dependence for the reaction of isopropyl alcohol 1a with methyl acrylate 2a to give 3a under O₂ (1 atm) using NHPI/Co(OAc)₂ I, NHPI/Co(acac)₃ II and NHPI/Co(OAc)₂/Co(acac)₃ III. 2a (3 mmol) was reacted with 1a (10 equiv.) in the presence of NHPI (10 mol%) under O₂ (1 atm), 60 °C in MeCN (0.5 mL). I: Co(OAc)₂ (1 mol%), II: Co(acac)₃ (1 mol%), III: Co(OAc)₂ (0.1 mol%) and Co(acac)₃ (1 mol%).

Table 1 Reaction of various alkenes CHR²=CR¹CO₂Me with 1a^a


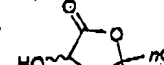

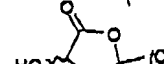

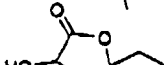

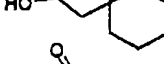

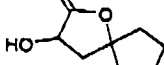

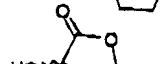
| Run | R ¹ | R ² | Alkene | T/°C | Yield of 3b–d (%) ^b |
|------------------|----------------|--------------------|-----------------|------|--------------------------------|
| 1 | Me | H | 2b | 70 | 71 (3b) |
| 2 | H | Me | 2c | 70 | 14 (74/26) ^c (3c) |
| 3 ^{d,e} | H | CO ₂ Me | 2d ^f | 25 | 90 (76/24) ^c (3d) |
| 4 ^d | H | CO ₂ Me | 2e | 25 | 86 (75/25) ^c (3d) |

^a 2 (3 mmol) was reacted with 1a (10 equiv.) under O₂ (1 atm) in the presence of NHPI (10 mol%), Co(OAc)₂ (0.1 mol%) and Co(acac)₃ (1 mol%) in MeCN (0.5 mL) for 8 h. ^b Isolated yield. ^c *trans/cis* ratio. ^d Reaction was carried out in the presence of Co(OAc)₂ (1 mol%) without Co(acac)₃. ^e 24 h. Air used. ^f Maleate.



Scheme 1

Table 2 Reaction of 2a with various alcohols

| Run ^a | Alcohol | t/h | Product ^b (%) |
|------------------|---|-----|--|
| 1 |  | 1† | 5  3f (74)[52/48] ^c |
| 2 |  | 1g | 8  3g (71)[80/40] ^c |
| 3 |  | 1h | 3  3h (83) |
| 4 ^d |  | 1h | 5  3h (78) |
| 5 |  | 1i | 8  3i (80) |
| 6 |  | 1j | 5  3j (41)[58/44] ^c |

^a 2a (3 mmol) was reacted with 1 (5 equiv.) in the presence of NHPI (10 mol%), Co(OAc)₂ (0.1 mol%) and Co(acac)₃ (1 mol%) under O₂ (1 atm) in MeCN (0.5 mL). ^b Isolated yield. ^c *trans/cis* ratio by GLC. ^d 1d (3 equiv.) used.

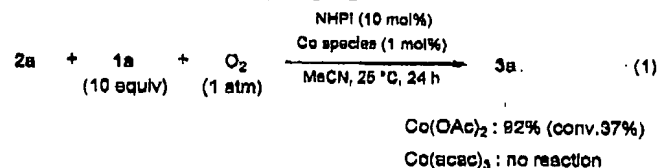
From α - and β -methyl substituted acrylates, methacrylate 2b and crotonate 2c, the corresponding α -hydroxy- γ -lactones, 3b and 3c, were obtained in 71 and 14% yields, respectively. The lower reactivity of 2c may be due to the β -CH₃ group which exerts steric hindrance towards the attacking radical Aa.⁹ Reactions with methyl maleate 2d and methyl fumarate 2e proceeded smoothly even at 25 °C to afford α -hydroxy- β -carbomethoxy- γ -lactone 3d in excellent yields, respectively. It is known that the incorporation of an electron-withdrawing substituent into the alkene decreases the SOMO-LUMO energy difference, and thus increases the rate of addition of alkyl radicals which possess nucleophilic reactivity.⁹

This new method for the construction of α -hydroxy- γ -lactones was quite general for a variety of alcohols (Table 2).[‡] From cyclic alcohols, α -hydroxy- γ -spirolactones, which so far have been very difficult to synthesize, were obtained in high yields. Like secondary alcohols, the primary alcohol, hexa-1-nol 1j, was found to generate the 1-hydroxyhexyl radical which then adds to 2a, giving the corresponding γ -lactone 3j (41%).

From viewpoints of low cost material, reaction efficiency and reaction simplicity, the present reaction is an innovative approach for the synthesis of α -hydroxy- γ -lactones which have considerable industrial potential.¹⁰

To gain further insight into the role of the cobalt species in the present reaction, the reaction of 1a with 2a by the NHPI/Co(II) system at room temperature was compared with that by the NHPI/Co(III) system [eqn. (1)]. The reaction via the NHPI/Co(II) system occurred at room temperature to give 3a in excellent selectivity (92%) at 37% conversion, while the same reaction with the NHPI/Co(III) system was not observed even after 24 h. These results indicate that the presence of Co(II) is

important to initiate the reaction. In a previous paper, we reported that a Co(III)-dioxygen complex derived from Co(II) species and O₂ accelerates the generation of PINO from NHPI.⁵ Efforts to expand this method and to elucidate the reaction mechanisms are currently in progress.



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Notes and references

[†] Typical procedure for the synthesis of α -hydroxy- γ -lactones 3a: to a solution of alcohol 1a (30 mmol), NHPI (0.3 mmol), Co(OAc)₂ (0.003 mmol) and Co(acac)₃ (0.03 mmol) in acetonitrile (0.5 mL) in a two-necked flask equipped a balloon filled with O₂ (1 atm) was added 2a (3 mmol). After the mixture was vigorously stirred at 60 °C for 5 h, rotary evaporation of the solvent and unreacted alcohol followed by flash chromatography on silica gel afforded dihydro-3-hydroxy-5,5-dimethyl-2(3H)-furanone 3a (78% yield).

[‡] The present reaction resulted in concomitant formation of oxidation products, ketones or aldehydes, of the alcohols in the range of 0.6 to 1.2-fold of the resulting lactones.

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